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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,628	03/05/2001	Arul M. Chinnaiyan	11203-005001/ UM 1850	4749

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GREGORY P. EINHORN
FISH & RICHARDSON P.C.
Suite 500
4350 La Jolla Village Drive
San Diego, CA 92122

EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	16

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,628	CHINNAIYAN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *1-50 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-59 and 61-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/02/02 (Paper No. 15), is acknowledged. Claims 1-75 are pending.

2. Claims 1-50 and 60 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. Claims 51-59 and 61-75 drawn to a method of *in situ* and *in vivo* imaging comprising a chimeric molecule which comprising RGD motif-comprising polypeptide of SEQ ID NO:1 and chemiluminescent polypeptide as the species *are under consideration in the instant application.*

4. In view of the amendment filed on 11/02/02, paper No. 15, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 51-59, and 61-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration of a pharmaceutical formulation which comprises a composition comprising a chimeric molecule wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 and the image is generated by computer assisted bioluminescent imaging (BLI) does not reasonably provide enablement for a method *in situ* or *in vivo* imaging of any cell, any tissue any organ or a full body comprising administration of any pharmaceutical formulation in an amount sufficient to enhance the image, wherein the pharmaceutical formulation comprises any composition comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 51, 52(a) 61, 62(a), 64, 65(a), 70 and 73, providing any imaging device as recited in claims 52(b), 62(b), 65(b), 71(b) and 74(b), administering the pharmaceutical formulation in an amount sufficient to generate the cell, tissue or body image as recited in claims 52(c), 62(c), 65(c), 70(c) and 74(c) and imaging the distribution of the pharmaceutical formulation with the imaging device, thereby imaging the cell, tissue or body as recited in claims 52(d), 62(d), 65 (d), 70 (d) and 74(d); the method further comprising providing any substrate in claim 57; or a method for *in vivo* imaging a tumor neovasculature in any individual comprising the following steps: providing any pharmaceutical formulation comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 59(a), 63(a), 66(a) and 72(a) providing any imaging device as recited in claims 59(b), 63(b), 66(b) and 72 (b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, paper No. 12, mailed 7/16/02.

Applicant's arguments, filed on 11-02-02, (Paper No. 15) have been fully considered but are not persuasive.

Applicant argue in conjunction with law cases that (a) the specification enabled the skilled artisan to make and use the claimed chimeric molecules, and provides examples of each of the components of claimed chimeric molecule (b) the RGD motifs and RGD-comprising polypeptides were also well known in the art at the time of the invention, and applicant asserts that RGD motifs are bound by molecules expressed on tumor cells, (c) as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of claim, then the enablement requirement of 35 U.S.C. 112 is satisfied, (d) applicant argues in conjunction with law case e.g. Hybritech, Inc. V. Monoclonal Antibodies, Inc. that the specification provides sufficient guidance for the skilled artisan to make and use a chimeric molecule comprising a RGD motif to detect RGD-binding polypeptides *in vivo,* analogous to *Hybritech*, furthermore, screening of RGD-motif comprising polypeptides would only have required routine screening, not undue experimentation.

While the Examiner acknowledged that the RGD motifs were well known in the art at the time of the invention, and RGD motifs are bound by surface integrin receptors expressed on endothelial cells. However, the specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated amino acids comprising "RGD motif-comprising polypeptide" encompassed by the claimed invention other than "SEQ ID NO: 1" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence comprising RGD motif and in turn utilizing predicted structural determinations to ascertain binding of RGD motifs to the integrins, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, "Comprises" in claims is open-ended, it expand the amino acid sequence of SEQ ID NO:1 to include additional

non disclosed amino acids outside of the "RGD motif" which does not provide that the peptide will retain the same binding activity as the SEQ ID NO:1. One of ordinary skill in the art cannot envision all of the amino encompassed by the breadth of the claims still having same recognition by integrins. Therefore, absent the ability to predict which of these molecules would function as claimed, and given the lack of data on changes critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Further, RGD-motif-comprising polypeptide is the primary site of recognition by integrins that are expressed on tumor cells and are responsible for tumor invasion. Therefore, there is insufficient direction and guidance as how the method for *in situ* or *in vivo* imaging of any cell, any tissue, any organ or any full body will be accomplished with the RGD-motif-comprising polypeptide.

Regarding the hybritech analogous case, Examiner notes that hybritech invention is drawn to monoclonal antibodies that specifically binds to specific antigen, however, applicant's invention is drawn to RGD motif-comprising polypeptides. Furthermore, in order to satisfy the U.S.C. 112, 1st paragraph, the specification has to teach how to make and/or use the invention, not how to screen to identify the invention. Until the time when RGD-comprising polypeptides are found, then one skill in the art can make them.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention with the different polypeptides as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

7. Claims 51-59, and 61-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, paper No. 12, mailed 7/16/02.

Applicant argues that an adequate written description is achieved since (1) the first domain of the chimeric molecule can be a fluorescent, bioluminescent polypeptide or a heterologous kinase, as well as exemplary species including aequorin, obelin, mnemiopsin, berovin, or herper simplex virus-1 thymidine kinase, (2) the second domain of the chimeric molecule can RGD motif-comprising polypeptide, a selecti-binding polypeptide, and the specification sets forth several exemplary species including those set forth in SEQ ID NO: 1-4.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the RGD motif-comprising polypeptide and it's binding function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of RGD-motif comprising polypeptides, wherein the RGD motif comprising polypeptides retain the features essential to the instant invention.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 51-59 and 61-75 are rejected under 35 U.S.C. 103(a) as being obvious over U.S Patent No. 5,650,135 (IDS reference AB), in view of U.S Patent No. 6,087,476 (IDS reference AA) and further in view of U.S Patent No. 6,180,084 for the same reasons set forth in the previous Office Action, paper No. 12, mailed 7/16/02.

Applicant argues that (1) there was no motivation for combining the references to arrive at the claimed methods, (2) the `135 patent discusses various non-invasive imaging compositions but are not those used in the claimed methods of the invention, (3) the `135 patent does not discuss or suggest a chimeric polypeptide of the invention, (4) the `476 patent discusses immunoglobulins, antigenic peptides, avidin, streptavidin, or protein A, while the `084 patent discusses tumor homing molecules, and (5) there is no suggestion or motivation in this patent to combine tumor homing molecules with a light emitting polypeptide to create a construct that can be imaged.

In response to applicant's argument that there was no motivation for combining the references to arrive at the claimed methods, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the resultant chimeric protein can be used to detect specific binding proteins taught by `476 which reflect in the presence of specific markers in endothelial cells taught by the `084 patent.

It is noted that applicant is attacking the references individually, however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

10. No claim allowed

11. Formal drawings have been submitted on 11/02/02 have fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

12. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink)

sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
December 30, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600